Dnmt3a regulates both proliferation and differentiation of mouse neural stem cells.

Journal: J Neurosci Res

Publication Year: 2012

Authors: Z Wu, K Huang, J Yu, T Le, M Namihira, Y Liu, J Zhang, Z Xue, L Cheng, G Fan

PubMed link: 22714992

Funding Grants: UCLA CIRM Research Training Program II

Public Summary:
DNA methylation is known to regulate cell differentiation and neuronal function in vivo. Here we examined whether deficiency of a de novo DNA methyltransferase, Dnmt3a, affects in vitro differentiation of mouse embryonic stem cells (mESCs) to neuronal and glial cell lineages. Early-passage neural stem cells (NSCs) derived from Dnmt3a-deficient ESCs exhibited a moderate phenotype in precocious glial differentiation compared with wild-type counterparts. However, successive passaging to passage 6 (P6), when wild-type NSCs become gliogenic, revealed a robust phenotype of precocious astrocyte and oligodendrocyte differentiation in Dnmt3a(-/-) NSCs, consistent with our previous findings in the more severely hypomethylated Dnmt1(-/-) NSCs. Mass spectrometric analysis revealed that total levels of methylcytosine in Dnmt3a(-/-) NSCs at P6 were globally hypomethylated. Moreover, the Dnmt3a(-/-) NSC proliferation rate was significantly increased compared with control from P6 onward. Thus, our work revealed a novel role for Dnmt3a in regulating both the timing of neural cell differentiation and the cell proliferation in the paradigm of mESC-derived-NSCs. (c) 2012 Wiley Periodicals, Inc.

Scientific Abstract:
DNA methylation is known to regulate cell differentiation and neuronal function in vivo. Here we examined whether deficiency of a de novo DNA methyltransferase, Dnmt3a, affects in vitro differentiation of mouse embryonic stem cells (mESCs) to neuronal and glial cell lineages. Early-passage neural stem cells (NSCs) derived from Dnmt3a-deficient ESCs exhibited a moderate phenotype in precocious glial differentiation compared with wild-type counterparts. However, successive passaging to passage 6 (P6), when wild-type NSCs become gliogenic, revealed a robust phenotype of precocious astrocyte and oligodendrocyte differentiation in Dnmt3a(-/-) NSCs, consistent with our previous findings in the more severely hypomethylated Dnmt1(-/-) NSCs. Mass spectrometric analysis revealed that total levels of methylcytosine in Dnmt3a(-/-) NSCs at P6 were globally hypomethylated. Moreover, the Dnmt3a(-/-) NSC proliferation rate was significantly increased compared with control from P6 onward. Thus, our work revealed a novel role for Dnmt3a in regulating both the timing of neural cell differentiation and the cell proliferation in the paradigm of mESC-derived-NSCs. (c) 2012 Wiley Periodicals, Inc.